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EXAMINER	
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1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/725,965	BUNTINX, ERIK	
	Examiner	Art Unit	
	UMAMAHESWARI RAMACHANDRAN	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41,42 and 78-85* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41,42 and 78-85* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/23/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner notes the receipt of the amendments and remarks received in the office on 4/23/2008 amending claims 41 and 42 and adding new claims 78-85. Claims 1-40, 43-77 have been canceled. Claims 41, 42, 78-85 are pending and are being examined on the merits herein.

Response to Remarks

Applicants' arguments regarding the rejection of claims 41 and 42 under 35 U.S.C. 103(a) as being unpatentable over Dudley et al. (US 2004/002482, effective filing date Mar 15 2002) in view of Squelart et al, (IDS: Applicant cited reference: Acta Psychiatr Belg, 1977, 77, 284-293), Medicaments Psychotropics (IDS: Applicant cited reference) and Coppen (U.S. 6,191,133) have been fully considered and found not to be persuasive. Addition of new claims, further search and consideration necessitated the new rejections presented in this office action. Accordingly, the action is made non-final.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 41, 78, 79 are rejected under 35 U.S.C. 102(b) as being anticipated by Wirz-Justice et al. (Applicant cited IDS reference: Alzheimer disease and associated disorders, 14(4), 212-215).

Wirz-Justice teaches combination medication of pipamperone 20-30mg/ml and citalopram 10 mg/ml (Table 1, p 214). Thus Wirz-Justice teachings anticipate the pharmaceutical composition of a compound having a selective affinity for the Dopamine-4 (D4) receptor with a pKi value equal to or higher than 8 towards the D4 receptor and less than 8 towards other Dopamine receptors, and a selective affinity for the 5-HT2A receptor with a pKi value equal to or higher than 8 towards the 5-HT2A receptor and less than 8 towards other 5HT receptors such as pipamperone and a selective serotonin re-uptake inhibitor such as citalopram as a combined preparation for simultaneous administration.

Note: Any properties exhibited by or benefits provided the composition are inherent and are not given patentable weight over the prior art. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties Applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure

would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and, (8) the quantity of experimentation necessary.

Claims 41, 42, 78, 79, 81-84 are rejected under 35 U.S.C. 112, first paragraph, because the specification and the prior art, while being enabling for a pharmaceutical composition comprising a compounds a compound having (i) a selective affinity for the Dopamine-4 (D4) receptor with a pKi value equal to or higher than 8 towards the D4 receptor and less than 8 towards other Dopamine receptors, and (ii) a selective affinity for the 5-HT2A receptor with a pKi value equal to or higher than 8 towards the 5-HT2A receptor and less than 8 towards other 5HT receptors (b) a selective serotonin re-uptake inhibitor, does not reasonably provide enablement for treating all the diseases or disorders listed in claim 41 and 81. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

(1, 5) The nature of the invention and the breadth of the claims:

The instant claims are directed to a pharmaceutical composition comprising a compound having (i) a selective affinity for the Dopamine-4 (D4) receptor with a pKi value equal to or higher than 8 towards the D4 receptor and less than 8 towards other Dopamine receptors, and (ii) a selective affinity for the 5-HT2A receptor with a pKi value equal to or higher than 8 towards the 5-HT2A receptor and less than 8 towards other

5HT receptors (Compound 1) (b) a selective serotonin re-uptake inhibitor (compound 2) for simultaneous, separate or sequential use for treating a disease or disorder with an underlying dysregulation of emotional functionality which is selected from the group consisting of mood disorders, anxiety disorders, schizophrenia and other psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders, factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, cognitive disorders, impulse control disorders, pervasive development, attention-deficit and disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational, identity, phase of life, academic problem, and problems related to abuse or neglect. The claims are very broad with respect to the compounds (41, 42, 80, 81, 82, 85) disease or disorders (41, 42, 78, 79, 81-84) and with respect to dosage. The dependent claims 78, 79, 82 and 83 are very narrowly defined with respect to the compounds and claims 80 and 85 with respect to the disease.

(3) The relative skill of those in the art:

The relative skill of those in the pharmaceutical and medical arts is high, requiring advanced education and training.

(4) The predictability of the art:

Despite the advance training of those in the art, the art is highly unpredictable. It is still not possible to predict the pharmacological activity or treatment efficacy of a compound based on the structure alone. It is also not possible to predict the efficacy of

a given class of compounds for the treatment of a particular disease absent a mechanistic link between the pharmacological activity of the class of agents and the etiology or pathophysiology of the disease. Typically, in order to verify that a compound will be effective in treating a disease, the compounds must be either tested directly in a patient or in a model that has been established as being predictive of treatment efficacy. In order to predict whether a class of compounds would be effective in treating a disease, the etiology or pathophysiology of the disease must be uncovered, and there should be a nexus between the pharmacological activity of the class of agents and the etiology or pathophysiology of the disease. Absent experimental tests verifying the efficacy of a compound or a strong nexus between the known pharmacological activity of a class of agents and the etiology and/or pathophysiology of the condition, it is impossible to predict whether the compound or class of compounds would actually be effective for treating the condition. In the instant case, the claims are directed to a comprising a compound having (i) a selective affinity for the Dopamine-4 (D4) receptor with a pKi value equal to or higher than 8 towards the D4 receptor and less than 8 towards other Dopamine receptors, and (ii) a selective affinity for the 5-HT2A receptor with a pKi value equal to or higher than 8 towards the 5-HT2A receptor and less than 8 towards other 5HT receptors (b) a selective serotonin re-uptake inhibitor for simultaneous, separate or sequential use for treating a disease or disorder with an underlying dysregulation of emotional functionality selected from the list of disorders (claim 41 and 81). The prior art (Atypical Antipsychotic Agents) teaches that fluoxetine and fluoxamine and sertraline may interfere with the metabolism of clozapine causing

an increased potential for adverse effects due to clozapine. Further the reference teaches that one case of tardive dyskinesia has been reported with concomitant use of fluoxetine and risperidone. Hence there is high unpredictability that all compounds claimed in claims 41 and 81 in a pharmaceutical composition will be useful in treating all the diseases and disorders listed.

(2) The state of the prior art:

The art recognizes (Marek et al.) the combination of 5-HT2A blocking agents and selective serotonin reuptake inhibitors exhibits synergistic action in neuropsychiatric disorders (abstract). The art (Marek et al.) recognizes the combination therapy of risperidone with SSRI in depression, obsessive compulsive disorders (OCD), autism etc. Marek et al. teaches other agents such as clozapine with SSRI's in the treatment of major depression, OCD. As stated above, Atypical Antipsychotic Agents teaches that fluoxetine and fluoxamine and sertraline may interfere with the metabolism of clozapine causing an increased potential for adverse effects due to clozapine. Further the reference teaches that one case of tardive dyskinesia has been reported with concomitant use of fluoxetine and risperidone.

(6, 7) The amount of guidance presented and the presence of working examples:

It has been established that, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." *In re Fisher*, 427 F.2d 833, 839 166 USPQ 18, 24 (CCPA 1970). Applicant has given guidance for the clinical trial set up for Pipamperon-Citalopram Treatment in Major Depressive Disorder and it is well known to

one of ordinary skill in the art that compound 1 and 2 can be obtained commercially. There are no examples provided in the specification formulating a pharmaceutical composition of compound 1 and 2 and no specific examples in using them for treating any of the disorders listed in claims 41 and 81. Though the prior art teaches the adjunct therapy with some combinations of compound 1 and compound 2, there is a high degree of unpredictability involved with respect to combining all the compounds of 1 with 2 and use them in treating every single disorder claimed in claims 41 and 81. A high degree of unpredictability is involved in combining two drugs as there may be drug interactions and if there are any adverse effects such combination may not be workable.

In summary, Applicant has provided little guidance beyond what was recognized in the art at the time of filing. Applicant has provided guidance for the clinical trial set up for Pipamperon-Citalopram Treatment in Major Depressive Disorder

(8) The quantity of experimentation needed:

In order to enable the instantly claimed methods commensurate with the entire scope, a large quantity of experimentation would be necessary. With Applicants' guidance provided in the specification and what is known in the prior art the person of ordinary skill in the art would have to conduct these experiments formulating each and every combination of compounds 1 and 2 as a combined preparation for simultaneous, separate or sequential for treating all the diseases claimed in claims 41 and 42. Considering the unpredictability of the combination of compounds due to their drug interactions, this would be an arduous and daunting task. Therefore, it would require

undue, unpredictable experimentation to practice the claimed invention of a formulating a pharmaceutical composition comprising a compound having (i) a selective affinity for the Dopamine-4 (D4) receptor with a pKi value equal to or higher than 8 towards the D4 receptor and less than 8 towards other Dopamine receptors, and (ii) a selective affinity for the 5-HT2A receptor with a pKi value equal to or higher than 8 towards the 5-HT2A receptor and less than 8 towards other 5HT receptors (b) a selective serotonin re-uptake inhibitor for simultaneous, separate or sequential use for treating every single disease or disorder with an underlying dysregulation of emotional functionality selected from the list of disorders in claims 41 and 81. Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 81-85 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 81 has a limitation "A pharmaceutical

composition consisting of" is new matter and does not have support in the specification. The specification teach a pharmaceutical composition 'containing' (para 009, abstract) or a pharmaceutical composition 'comprising' (para 011, claims 41, 42). The specification does not teach anywhere including examples a composition consisting of compound having (i) a selective affinity for the Dopamine-4 (D4) receptor with a pKi value equal to or higher than 8 towards the D4 receptor and less than 8 towards other Dopamine receptors, and (ii) a selective affinity for the 5-HT2A receptor with a pKi value equal to or higher than 8 towards the 5-HT2A receptor and less than 8 towards other 5HT receptors (b) a selective serotonin re-uptake inhibitor. The specification teaches a pharmaceutical composition comprising or containing compounds 1 and 2 but not consisting compounds 1 and 2 as defined above. Applicants' state in the arguments dated 4/23/2008 that support for new claims 81 and 85 can be found at least in claims 41 and 42 and 78-80 but the claims 41 and 42 and the depending claims 78-80 are all directed to a pharmaceutical composition 'comprising' compound 1 and 2.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 41, 42 and 80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dudley et al. (US 2004/002482, effective filing date Mar 15 2002) in view of Wirz-Justice et al. (Applicant cited IDS reference: Alzheimer disease and associated disorders, 14(4), 212-215) and Medicaments and Psychotropes (Applicant cited IDS reference).

Dudley et al. teach combinations and compositions for treating or preventing or reducing the risk of developing a depressive disorder (a mood disorder) or the symptoms associated with the disorder comprising compounds such as citalopram, pipamperone (see abstract, para 0132, lines 14 and 42). Dudley et al. teach citalopram and pipamperone as antidepressants (para 0132). The reference teach that the combinations of the antidepressant agents can be used in the methods, kits, combination and compositions (para 0132, p 10, lines 5-7).

Although, Dudley et al does not explicitly teach both citalopram and pipamperone in the same composition it would have been obvious to one of ordinary skill in the art at the time of the invention to formulate a composition comprising both the compounds in the same composition because Dudley suggest the composition and combination of the compounds and further teach the compounds are useful as antidepressant agents. One of ordinary skill in the art at the time of the invention would have been motivated to formulate such a composition in expectation of success as well to achieve synergistic

and or additive benefits from deriving such a formulation as both the compounds are taught to be useful as antidepressant agents.

Dudley does not explicitly teach the dose of the antidepressant compounds in the composition.

Wirz-Justice teaches combination medication of pipamperone 20-30mg/ml and citalopram 10 mg/ml (Table 1, p 214).

Medicaments and Psychotropes document teaches that an initial dose of 10 mg dipiperon can be administered.

It would have been obvious to one of ordinary skill in the art at the time of the invention to formulate a pharmaceutical composition comprising a compound having (i) a selective affinity for the Dopamine-4 (D4) receptor with a pKi value equal to or higher than 8 towards the D4 receptor and less than 8 towards other Dopamine receptors, and (ii) a selective affinity for the 5-HT2A receptor with a pKi value equal to or higher than 8 towards the 5-HT2A receptor and less than 8 towards other 5HT receptors such as pipamperone (b) a selective serotonin re-uptake inhibitor, citalopram because Dudley teach both the compounds to be antidepressants, Wirz-Justice teaches combination therapy comprising citalopram and pipamperone. One of ordinary skill in the art would have been motivated to incorporate the agents herein in a single combination pharmaceutical composition because combining the agents herein each of which is known to be useful to treat mental disorders including depression individually into a single composition useful for the very same purpose is *prima facie* obvious. See *In re*

Kerkhoven 205 USPQ 1069. Also, one of ordinary skill in the art would have expected success as Wirz-Justice teaches both the compounds in a treatment.

It would have been obvious to one of ordinary skill in the art at the time of the invention to formulate a composition comprising such compounds in an amount range as claimed in claim 42 because Wirz-Justice teaches combination medication of pipamperone 20-30mg/ml and citalopram 10 mg/ml, Medicaments and Psychotropes document teaches that an initial dose of 10 mg dipiperon can be administered. Also, the amount of an ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal amount of ingredient to add in order to best achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, this optimization of ingredient amount would have been obvious at the time of applicant's invention.

Claims 81-85 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bymaster et al. (Applicant cited IDS reference: WO 98/11897) and Wirz-Justice et al. (Applicant cited IDS reference: Alzheimer disease and associated disorders, 14(4), 212-215) and Marek et al. (Neuropsychopharmacology, 1991, 28, 402-412) and Medicaments and Psychotropes (Applicant cited IDS reference).

Bymaster et al. teaches a pharmaceutical composition comprising a first component an antipsychotic and a second compound a serotonin reuptake inhibitor.

The reference for example, teaches a risperidone/fluoxetine pharmaceutical composition (p 6) as a combination and teaches several examples of combinations of various antipsychotic and serotonin reuptake inhibitor compounds (See examples). The reference further teach that the antipsychotic agents while improving the lives of psychotic patients immeasurably, may not be sufficient to treat every psychotic patient as psychotic conditions appear to have a complex etiology, some schizophrenics which exhibit depressive episodes or depressed individuals which also have psychotic episodes may not find total relief using only one atypical psychotic agent (p 1, lines 25-30). The reference teaches that the adjunctive therapy of antipsychotic agent with a serotonin reuptake inhibitor provides a potentiation of the increase in the concentration of norepinephrine observed as an effect of administration of a first component compound by administration of a second component compound (p 24, lines 1-5).

Marek et al. teach the combination of 5-HT2A blocking agents and selective serotonin reuptake inhibitors exhibits synergistic action in neuropsychiatric disorders (abstract).

Wirz-Justice et al teaches combination medication of pipamperone 20-30mg/ml and citalopram 10 mg/ml (Table 1, p 214).

Medicaments and Psychotropes document teaches that an initial dose of 10 mg dipiperon can be administered

The references do not teach explicitly teach the pharmaceutical composition consisting of citalopram and pipamperone.

It would have been obvious to one of ordinary skill in the art at the time of the invention to have formulated a pharmaceutical composition consisting an antipsychotic agent and a serotonin reuptake inhibitor from the teachings of Bymaster et al. The reference teaches a pharmaceutical composition consisting antipsychotic agents with serotonin reuptake inhibitors. The reference further teach that the antipsychotic agents while improving the lives of psychotic patients immeasurably, may not be sufficient to treat every psychotic patient as psychotic conditions appear to have a complex etiology, some schizophrenics which exhibit depressive episodes or depressed individuals which also have psychotic episodes may not find total relief using only one atypical psychotic agent. The reference teaches that the adjunctive therapy of antipsychotic agent with a serotonin reuptake inhibitor provides a potentiation of the increase in the concentration of norepinephrine observed as an effect of administration of a first component compound by administration of a second component compound. One having ordinary skill in the art would have been motivated to formulate a pharmaceutical composition consisting of citalopram and pipamperone because of expectation of success from Wirz-Justice et al's teachings, to relieve the depression in psychotic patients and a potentiation to increase the concentration of norepinephrine as an effect of administration of a first component compound by administration of a second component compound as taught by Bymaster et al. and further because of the synergistic effects in combining the 5-HT2A blocking agents and selective serotonin reuptake inhibitors as taught by Marek et al.

It would have been obvious to one of ordinary skill in the art at the time of the invention to formulate a composition comprising such compounds in an amount range as claimed in claim 82 because Wirz-Justice teaches combination medication of pipamperone 20-30mg/ml and citalopram 10 mg/ml, Medicaments and Psychotropes document teaches that an initial dose of 10 mg dipiperon can be administered. Also, the amount of an ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal amount of ingredient to add in order to best achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, this optimization of ingredient amount would have been obvious at the time of applicant's invention.

Response to Arguments

Applicants' argue that that the use of daily low dose between 5- 15 mg of pipamperone augments the effect of SSRI in treating a disorder. In response, the claims of the instant invention are directed towards a formulation and not to a method of treatment. The prior art including Dipiperon teaches a daily dose of 20 mg of Pipamperone administered to children. The instant claim teaches up to 15 mg of pipamperone. The amount of an ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. In addition the prior art, Marek et al. teach the combination of 5-HT2A blocking agents and

selective serotonin reuptake inhibitors exhibits synergistic action in neuropsychiatric disorders. Hence one of ordinary skill in the art would have been motivated to add less amounts of the drugs in combination in expectation of synergistic effects.

Applicants' argue that Dudley teaches compositions and combinations comprising a steroid and provides an alternative for subjects failing to respond to conventional antidepressants. In response, the claims of the instant invention are directed towards a pharmaceutical composition "comprising" which does not limit the claims only to the compounds listed in the claims.

Applicants' argue that Dudley does not teach any combination having a beneficiary effect. In response, Dudley teach both citalopram and pipamperone are antidepressants. Hence one having ordinary skill in the art would have been motivated to combine drugs that are useful for the same treatment in expectation of success, in expectation of synergistic or additive therapeutic benefits.

Applicants' argue that Pipamperone is mischaracterized in Dudley, Pipamperone is recommended as a neuroleptic agent. Dudley teach the compound pipamperone as antidepressant and so as other prior art such as Marek et al. (p 406, col. 2, lie 35).

Applicants' provide Dipiperon and state that the instructions on the manufacturer teach against the combination. In regards to the arguments of "4.3 Contraindications-Depression of the central nervous system" (emphasis added)., and "4.4 Special warnings and precautions for use - ...Maior Depression can become visible as a result of antipsychotics. A mood may arise as a result of taking antipsychotics that is difficult to distinguish from depressive symptoms", *"4.8* Undesirable effects: The following side

effects may also occur: convulsions, worsening of depressions and dysphoria and malignant neuroleptic syndrome (see special warnings and precautions for use) ." These are instructions given for taking the drug pipamperone (dipiperon) and not for taking a combination of drugs with pipamperone. In regards with the interactions of pipamperone with other medicinal products and other forms of interaction Applicants state the following and argue that the instructions on the manufacturer teach against the combination. -..The simultaneous use of other antipsychotics, lithium, antidepressants, anti-Parkinson medicines and drugs with a central anticholinergic, effect increases the risk of the occurrence of tardive dyskinesia (TD)" (Emphasis added.). In response, Dipiperon teach that Tardive Dyskinesia "may" occur in long term treatment with antipsychotics (especially at high doses). In fact, Dipiperon teaches that administration of dipiperon alone may cause TD after a long term treatment and further state that it increases the risk of occurrence of tardive dyskinesia when co-administered with agents like antidepressants but does not teach against or away from combining antidepressants with pipamperone. In fact the prior art, Wirz-Justice et al teaches a combination medication of pipamperone 20-30mg/ml and citalopram 10 mg/ml and Bymaster et al. teaches combination of antipsychotics with antidepressants as adjunct therapy and Marek et al. teach the synergistic effects of combining them.

Any rejection of record not addressed herein is withdrawn.

Conclusion

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Umamaheswari Ramachandran whose telephone number is 571-272-9926. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SREENI PADMANABHAN/
Supervisory Patent Examiner, Art Unit 1617